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Appraisal of a glycopeptide cloaking strategy for a therapeutic oligopeptide: glycopeptide analogs of the renin inhibitor ditekiren.

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Among the limitations to the practical therapeutic oligopeptide are low oral availability, indifferent aqueous solubility, and an astonishing efficient sequestration and biliary elimination by a multi-capacity liver transporter. Given the purposed use of N- and O- linked saccharides as functional appendages of eukaryotic peptides and proteins, a strategy of glycopeptide mimicry was examined for the oligopeptide renin inhibitor, ditekiren. The anticipation was that the saccharide would impart significant aqueous solubility, and might impact beneficially on the remaining two limitations. Execution of this approach was achieved by the removal of the (dimethylethoxy)carbonyl amino terminus of ditekiren, and its substitution by Boc-L-asparagine N-linked mono- and disaccharides. Potent hypotensive activity, as measured by a human renin-infused rat assay, is observed for virtually all of these structures (N-linked beta-pyranose D-N-acetyglucosaminyl, D-glucosaminyl, D-N-acetylgalactosaminyl, D-mannosyl, D-galactosyl, D-maltosyl, D-cellobiosyl, D-chitobiosyl, but not L-fucosyl). The basis for this dramatic improvement (relative to ditekiren in the same assay) is the diversion of the peptide clearance from rapid liver biliary clearance to slower urinary clearance (Fisher, J. F.; Harrison, A. W.; Wilkinson, K. F.; Rush, B. R.; Ruwart, M. J. J. Med. Chem. 1991, 34, 3140). Guided by the human renin-infused rat hypertension assay, an evaluation of the linker-saccharide pairing was made. Loss of hypotensive activity is observed upon substitution of the Boc-L-asn by Boc-D-asn, and by removal of the Boc amino terminus of the glycopeptide. Potent hypotensive activity is preserved by replacement of the Boc-L-asn linker by succinate, malate, tartrate, and adipate linkers. With the longer adipate spacer, attachment of the saccharide to the P-3 phenylalanine--with omission of the P-4 proline--retains activity. These data suggest value to the glycopeptide guise for preserving the in vivo activity, and for the beneficial manipulation of pharmacodynamics, of this renin inhibitory oligopeptide. This strategy may have general applicability.

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